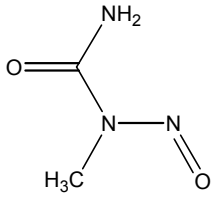
N-NITROSO-*N*-METHYLUREA
CAS No. 684-93-5
First Listed in the *Second Annual Report on Carcinogens*



CARCINOGENICITY

N-Nitroso-*N*-methylurea is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity in experimental animals (IARC V.1, 1972; IARC V.17, 1978; IARC S.4, 1982; IARC S.7, 1987). When administered in the diet, *N*-nitroso-*N*-methylurea induced squamous cell carcinomas of the forestomach, sarcomas and gliomas of the brain, and neurosarcomas in rats. When administered in the drinking water, *N*-nitroso-*N*-methylurea induced tumors of the brain (mainly gliomas), and one neurinoma of the spinal cord in rats; in guinea pigs it induced carcinomas and sarcomas of the stomach, adenocarcinomas of the pancreas, malignant tumors of the ear duct, one neurinoma of the lumbar nerve, and leukemia. When administered intragastrically, *N*-nitroso-*N*-methylurea induced malignant tumors of the kidney, forestomach, small and large intestines, skin, and jaw in rats; odontogenic tumors and epidermoid carcinomas of the oral cavity, and adenocarcinomas of the small and large intestines in hamsters; and adenocarcinomas of the pancreas, stomach, and colon, lymphomas of the mesenteric lymph nodes, and one hepatocellular carcinoma in guinea pigs. When administered orally, the chemical induced malignant tumors of the stomach in pigs and squamous cell carcinomas of the oropharynx and/or esophagus in monkeys. When administered topically, *N*-nitroso-*N*-methylurea induced leukemia and malignant skin tumors (including papillomas) in mice; squamous and basal cell carcinomas of the skin in rats; and squamous cell carcinomas of the skin in hamsters. When administered by intratracheal instillations, *N*-nitroso-*N*-methylurea induced epidermoid carcinomas in the nasopharyngeal tube, pharynx, larynx, trachea, bronchi, esophagus, and forestomach, and large cell anaplastic carcinomas of the trachea in hamsters. When administered by subcutaneous injection, the chemical induced lymphomas, local sarcomas, lymphosarcomas involving the thymus, myocardium, lung, spleen, lymph nodes, liver, kidney, and bone marrow, leukemias, and pulmonary tumors in mice; nervous system tumors in rats; and local sarcomas, fibrosarcomas, carcinosarcomas, and epidermal carcinomas and papillomas of the forestomach in hamsters. When administered by intraperitoneal injection, *N*-nitroso-*N*-methylurea induced thymic lymphomas, pulmonary adenomas, lymphosarcomas, lung adenomas, hepatomas, and bronchial adenomas in mice; malignant tumors in the peritoneal cavity, lymphosarcomas, intestinal adenocarcinomas, and mammary tumors in rats; adenocarcinomas of the large and small intestines in hamsters; and adenocarcinomas of the pancreas, fibrosarcomas, angiosarcomas of the mesentery, one mesothelioma of the peritoneum, tumors of the small intestine, and one hemangiosarcoma of the liver in guinea pigs. Intravenous administration of *N*-nitroso-*N*-methylurea induced leukemia in mice and malignant tumors of the brain (gliomas, ependymomas, medulloblastomas, and intracranial sarcomas), spinal cord (spongioblastomas, medulloblastomas, and gliomas), peripheral nervous system neurinomas, mammary carcinomas, astrocytomas, oligodendrogliomas, anaplastic gliomas, gliosarcomas, and differentiated and anaplastic neurinomas in rats. Intravenous administration of *N*-nitroso-*N*-methylurea also induced adenocarcinomas of the small and large intestines, odontogenic tumors, epidermoid carcinomas of the oral cavity, sarcomas of the heart, and squamous cell carcinomas of the stomach in hamsters; carcinomas and papillomas of the oral cavity, and carcinomas and

adenomas of the midventral sebaceous gland in gerbils; polymorphous gliomas and sarcomas, carcinomas and adenocarcinomas of the small intestine, vascular and central nervous system tumors, malignant hemangioendotheliomas of the lung, spleen, and heart, and anaplastic neurinomas in various organs in dogs. Prenatal exposure by injection of *N*-nitroso-*N*-methylurea induced pulmonary adenomas and hepatomas in the offspring of mice. When administered by urethral catheterization, *N*-nitroso-*N*-methylurea induced papillomas and transitional cell carcinomas of the bladder in female rats. Intrarectal administration of *N*-nitroso-*N*-methylurea induced adenomas and adenocarcinomas of the distal colon and rectum, squamous cell carcinomas of the anal canal, and lung adenomas and lymphomas in mice; large bowel adenomas, adenocarcinomas, and carcinomas in male rats; and large bowel adenocarcinomas in female guinea pigs. When administered by intracerebral injection, *N*-nitroso-*N*-methylurea induced kidney fibrosarcomas and one mammary gland carcinoma in rats and leukemia and pulmonary tumors in mice (IARC S.4, 1982; IARC V.17, 1978; IARC V.1, 1972).

There are no data available to evaluate the carcinogenicity of *N*-nitroso-*N*-methylurea in humans (IARC S.4, 1982).

PROPERTIES

N-Nitroso-*N*-methylurea is composed of large pale yellow crystals. It is soluble in water and polar organic solvents and insoluble in nonpolar organic solvents. It degrades readily in the presence of ultraviolet or visible light. It is potentially explosive at room temperature. When heated to decomposition, it emits toxic fumes of nitrogen oxides (NO_x).

USE

N-Nitroso-*N*-methylurea has been used to synthesize diazomethane in the laboratory, but other reagents have replaced it to a large extent. *N*-Nitroso-*N*-methylurea has been used extensively in mutagenicity and genetics studies and as a chemotherapeutic agent in cancer treatment, either alone or in combination with cyclophosphamide (see also Cyclophosphamide, Section III.A). Commercial use of *N*-nitroso-*N*-methylurea is not known (IARC V.17, 1978).

PRODUCTION

The Chem Sources USA directory identified two producers and six suppliers of *N*-nitroso-*N*-methylurea in 1986 (Chem Sources, 1986). No other current production data were available. The 1979 TSCA Inventory identified one producer of *N*-nitroso-*N*-methylurea in 1977 with a reported production of 500 lb (TSCA, 1979). No evidence has been found that it has been produced in significant commercial quantities (IARC V.17, 1978). No import or export data were available.

EXPOSURE

The primary routes of potential human exposure to *N*-nitroso-*N*-methylurea are injection, inhalation, and dermal contact. In air it exists solely as vapor. It hydrolyzes in water (half-life 1.2 hours at pH=7 at 20^{o}C. Workers may possibly be exposed to *N*-nitroso-*N*-methylurea during its production. A limited number of research laboratory workers may also be possibly exposed; several accidents have been reported in which laboratory personnel were exposed when the

compound exploded at room temperature. Potential for direct exposure is through injection of cancer patients with *N*-nitroso-*N*-methylurea in conjunction with cyclophosphamide, as a chemotherapeutic agent, but there are no reliable data on the frequency or extent of this use. Health professionals (e.g., physicians, nurses) are potentially exposed to the compound during the preparation and administration of the pharmaceuticals or during clean-up.

REGULATIONS

EPA regulates *N*-nitroso-*N*-methylurea under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), Resource Conservation and Recovery Act (RCRA), and Superfund Amendments and Reauthorization Act (SARA). EPA has established a final rule reportable quantity (RQ) of 1 lb for *N*-nitroso-*N*-methylurea under CERCLA. EPA has promulgated report/recordkeeping requirements for this chemical under RCRA and SARA. OSHA regulates *N*-nitroso-*N*-methylurea under the Hazard Communication Standard and as a chemical hazard in laboratories. Regulations are summarized in Volume II, Table B-106.